Biobehavioral Factors and Cancer Progression: Physiological Pathways and Mechanisms

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Epidemiologic evidence increasingly has supported the role of biobehavioral risk factors such as social adversity, depression, and stress in cancer progression. This review describes in vitro, in vivo, and clinical studies demonstrating relationships between such processes and pathways involved in cancer progression. These include effects on the cellular immune response, angiogenesis, invasion, anoikis, and inflammation. Biobehavioral factors have been shown to contribute to the cross talk between tumor and host cells in the tumor microenvironment, and stress effects on host cells such as macrophages seem to be critical for many pathways involved in tumor progression. Some effects are bidirectional in that tumor-derived inflammation seems to affect central nervous system processes, giving rise to vegetative symptoms and contributing to dysregulation of the hypothalamic-pituitary-adrenal axis with downstream effects on inflammatory control. Findings to date are reviewed, and fruitful areas for future research are discussed. **Key words:** biobehavioral, stress, cancer, social support, angiogenesis.

HPA = hypothalamic-pituitary-adrenal; **ECM** = extracellular matrix; **MMP** = matrix metalloproteinase; **CNS** = central nervous system; **NK** = natural killer; **TIL** = tumor-infiltrating lymphocyte; **VEGF** = vascular endothelial growth factor; **IL** = interleukin; **NE** = norepinephrine; **TAM** = tumor-associated macrophage; **FAK** = focal adhesion kinase.

INTRODUCTION

Ever since the time of the ancient Greeks, there has been an interest in the relationship between psychological states and cancer (1). Epidemiologic studies have highlighted several key psychological factors related to both cancer initiation (development of cancer in patients with no previous tumor) and progression (expansion of disease in patients with existing cancers). The most commonly studied factors have been chronic stress, depression/distress, and social support/isolation. Epidemiologic data supporting a potential role of psychological factors as related to cancer initiation have been relatively equivocal (2–4), with the most consistent evidence pointing to a relationship of cancer incidence with severe life events, severe distress, or long-term depression (5,6). A more consistent association has been observed between psychosocial risk factors such as depression (7–9), distress (10), trauma history (11), social isolation (12–14), and more rapid cancer progression. Recent meta-analyses have linked depression (15), stressful life events (10,16), and social isolation (17) with poorer survival in patients with cancer. Although not all findings are consistent (18,19), the predominance of epidemiologic evidence supports a relationship between psychosocial factors and cancer progression. Thus, this review will focus on data related to cancer progression.

MODEL OF THE SOCIOENVIRONMENTAL MACROENVIRONMENT AND CANCER PROGRESSION

A conceptual model has been proposed linking socioenvironmental factors in the "macroenvironment" and cancer progression (20). According to this model, central nervous system (CNS) perceptions of threat from environmental stressors, such as negative life events, socioeconomic burden, relationship difficulties, social isolation, and so on, interact with an individual's characteristic attitudes, perceptions, and coping abilities, resulting in conditions such as perceived stress, distress, loneliness, and the like. These states, particularly when experienced chronically, lead to downstream activation of neuroendocrine pathways including the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Catecholamines, glucocorticoids, and other stress hormones and neuropeptides (e.g., oxytocin, dopamine) are released via the brain, the sympathetic nervous system, and/or the HPA axis. Neuroendocrine stress hormones in the tumor microenvironment assert a systemic influence on tumor growth. Psychosocial factors such as active coping, resilience, optimism, and social support may act to buffer the elicitation of the stress response. It should be noted that, although psychology has elaborated definite distinctions between constructs such as "stress," "distress," "depression," and "social isolation" at this point in the development of biobehavioral oncology research, the biological signatures of these various constructs have not been well differentiated with respect to processes at the tumor level. The preclinical studies generally use stress-related paradigms. Thus, we have adopted the relatively imprecise approach of describing constructs such as depression and social isolation along with stress as "biobehavioral risk factors" to convey the general phenomenon that biobehavioral processes seem to systematically affect a variety of important hallmarks of cancer biology. Because most of the emerging work described later has involved the sympathetic nervous system and the HPA axis, discussion will focus on these two stress response systems;

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however, it is likely that a variety of other neuroendocrine hormones may also influence the biological processes described later.

Early research examining CNS effects on cancer predominantly focused on downregulation of the immune response as a potential mediator of impaired surveillance for metastatic spread (21–25). Other work focused on stress effects on DNA repair (26,27). Given the unlikely role of a singular system in explaining the biological effects of stress pathways on cancer progression, during the last 10 years, the focus of mechanistic biobehavioral oncology research has broadened to include examination of the effects of stress on a) tumor angiogenesis, b) invasion and anoikis, c) stromal cells in the tumor microenvironment, and d) inflammation.

BIOBEHAVIORAL FACTORS AND THE CELLULAR IMMUNE RESPONSE IN CANCER PROGRESSION

Substantial evidence has demonstrated that negative psychosocial states, such as chronic stress, depression, and social isolation, are associated with downregulation of the cellular immune response, mediated largely by adrenergic and glucocorticoid signaling (28–30). For example, among patients with breast cancer, after surgery, low levels of social support and distress have been linked with decrements in indicators of cellular immunity, including impaired natural killer (NK) cell cytotoxicity (31–33), blunted T-cell production of T helper 1 versus T helper 2 cytokines (34), and decreased T-cell proliferative response to mitogens (33). Depression has also been associated with a poorer cellular immune response to specific antigens in patients with breast cancer (35). It should be noted, however, that not all findings have been consistent in this literature (e.g., Von et al. (36)).

Tumors have well-developed escape mechanisms by which they interfere with immune cell signaling and thus evade recognition and destruction by the immune response (37,38). Thus, the immune response in the tumor microenvironment is substantially downregulated compared with that in peripheral blood. We therefore considered whether stress-related influences would operate within the tumor microenvironment. Among patients with ovarian cancer at the time of surgery, NK cell activity in tumor-infiltrating lymphocytes (TILs) was diminished by more than 50%, compared with NK cell activity in lymphocytes isolated from peripheral blood, reflecting substantial downregulation. Nevertheless, biobehavioral factors were related to the cellular immune response in TIL. Specifically, social support was related to greater NK cell activity in both peripheral blood and TIL, whereas distress was associated with blunted NK cell activity in TIL and poorer T-cell production of T helper 1 versus T helper 2 cytokines in peripheral blood, ascites, and TIL (39,40). These findings suggest that biobehavioral risk factors do have some association with immune activity in the tumor microenvironment and underscore the importance of examining associations between biobehavioral factors and immune cells directly in the tumor microenvironment.

One issue that bears further comment is the extent to which relationships with markers of the immune response are predictive of disease recurrence and survival. This question has been difficult to investigate because of the large sample size and the relatively extensive follow-up required. One study reported that depressed patients with hepatobiliary carcinoma had lower NK cell numbers and shorter survival compared with their nondepressed counterparts and that NK cell count mediated the relationship between depression and survival (7). However, in general, the extent to which stress-related changes in the immune response are relevant for recurrence and survival is still unclear, and biobehavioral survival studies among patients with breast cancer have not reported a mediating role for NK cell activity (23,41).

Preclinical experimental studies with animal models have demonstrated similar patterns. For example, stress-induced release of catecholamines and prostaglandins, particularly in the perisurgical period, have been shown to suppress key components of the cellular immune response, including NK cell activity, which may allow for more aggressive course of disease (42–47).

ANGIOGENESIS AND INVASION

Cancer-related mortality largely results from the spread of cancer cells from the primary tumor to other sites in the body, a process called *metastasis*. Successful metastatic spread requires several sequential steps, including angiogenesis, proliferation, invasion, embolization, and colonization of a new secondary site (48). Many of these steps involve complex signaling interactions with surrounding cells. Stress response pathways have now been shown to influence many parts of this cascade including activities of both stromal and tumor cells (Fig. 1).

Tumor growth and metastatic spread are dependent on the development of adequate vascularization, a process called *angiogenesis*. This process is tightly controlled by a variety of positive and negative factors secreted by both tumor and host cells in the tumor microenvironment (49,50). Angiogenesis-promoting factors include vascular endothelial growth factor (VEGF), interleukin (IL) 6, IL-8, tumor necrosis factor α, and a variety of other molecules (51,52). In vitro, in vivo, and clinical studies have demonstrated links between biobehavioral factors and angiogenic pathways. For example, among patients with ovarian cancer at the time of surgery, higher levels of social support were associated with lower levels of VEGF both in serum (53) and in tumor tissue (54). Similarly, among patients with colon cancer, loneliness was related to higher levels of tumor VEGF at the time of surgery (55), and depression and poor quality of life were associated with higher level of serum VEGF both before and 6 weeks after surgery (56). Each of these studies controlled for relevant clinical variables. In vitro experiments in ovarian, melanoma, myeloma, and nasopharyngeal cancer cell lines have demonstrated that norepinephrine (NE) and the β-agonist isoproterenol profoundly stimulated

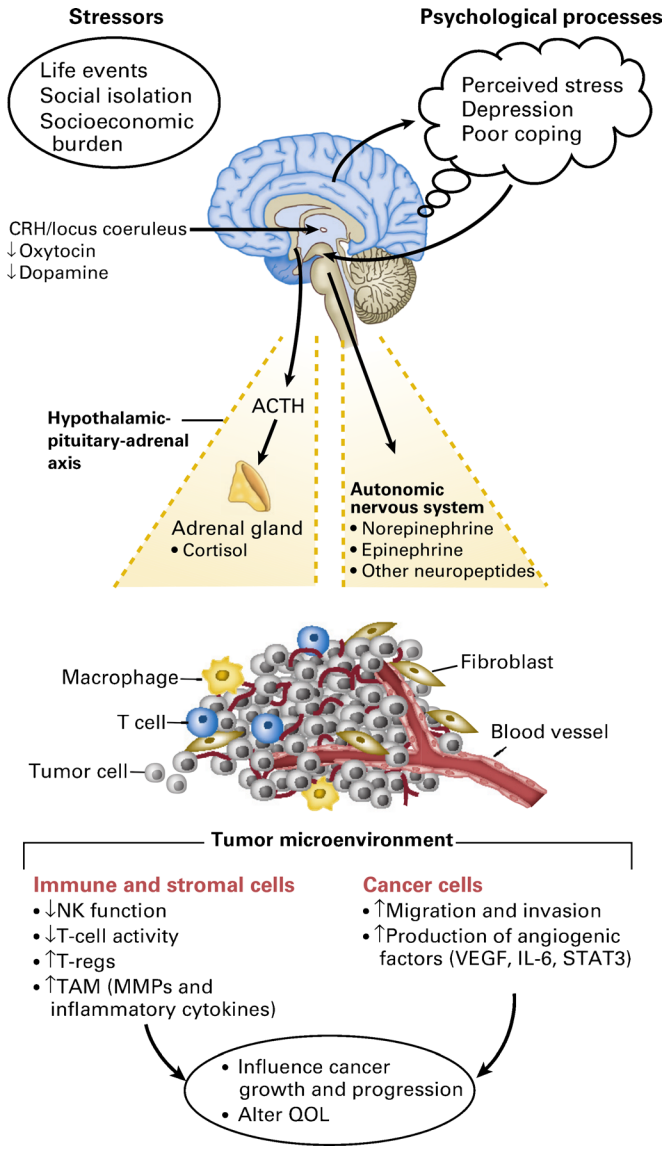

Figure 1. Effects of stress and psychosocial processes on the tumor microenvironment. The stress response results in activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis. Factors released from these pathways can have direct effects on the tumor microenvironment, resulting in a favorable environment for tumor growth and progression. These dynamics can also adversely affect patient's quality of life. CRH = corticotrophin-releasing hormone; ACTH = adrenocorticotrophic hormone; NK = natural killer; T-regs = regulatory T cells; TAM = tumor-associated macrophage; MMPs = matrix metalloproteinases; VEGF = vascular endothelial growth factor; IL = interleukin; STAT3 = signal transducer and activator of transcription factor 3; QOL = quality of life. Reprinted with permission from Lutgendorf et al. (J Clin Oncol 2010;28:4094–9). Copyright 2010, American Society of Clinical Oncology.

expression of VEGF, which was blocked by the β-blocker propranolol (57–61). Further support for these pathways has come from preclinical experiments with orthotopic mouse models of ovarian cancer. Both chronic restraint stress and surgical stress have been shown to increase ovarian tumor weight and invasiveness—changes that were mediated by NE-driven increases in VEGF and angiogenesis (61,62). These effects were completely blocked by propranolol, a nonspecific β-blocker, thus confirming the role of adrenergic signaling underlying these effects. Social isolation has been shown to have similar effects on tumor weight and invasiveness (61).

IL-6 is another cytokine that plays a key role in tumor angiogenesis, attachment, and invasion. It is produced by tumor cells and tumor-associated macrophages (TAMs) (63,64). Elevated IL-6 levels were observed in both plasma and ascites (the malignant effusions surrounding tumors) in patients with advanced stage ovarian cancer with low levels of social support, thus paralleling the VEGF findings described previously (65). Stress hormones such as NE have been shown to induce production of IL-6 and IL-8 by ovarian cancer and melanoma cells (59,63), demonstrating effects of stress response pathways on tumor-signaling mechanisms. Consistent with these findings, we have observed elevated levels of tumor, but not plasma, NE among patients with low levels of social support, suggesting the possibility that these social support findings may be adrenergically mediated at the tumor level (66).

The ability of tumor cells to detach from the primary tumor, invade through the basement membrane, and enter the vascular system is another critical step in the metastatic cascade. Matrix metalloproteinases (MMPs) are enzymes secreted by both tumor and stromal cells that facilitate the breakdown and remodeling of the extracellular matrix (ECM), thus enabling both local and distal tumor spread (67). Stress hormones promote the migration and invasion of tumor cells in multiple ways, including stimulation of MMP production by both stromal and tumor cells. Levels of NE commensurate with those that would be observed during the stress response have been shown to increase the in vitro invasive potential of ovarian cancer cells by 89% to 198%, a process that was blocked by propranolol (68). This effect was mediated by increased MMP-2 and MMP-9 levels in response to NE (68). Similar biological effects have been reported in several other tumor types including colon and head and neck cancers (58,69–71).

Stress Effects on Anoikis

Cells other than hematopoietic cells are anchorage dependent and normally survive only when adhering to the ECM. Anoikis is the normal process of programmed cell death (apoptosis) occurring when anchorage-dependent cells become separated from the ECM. Cancer cells acquire the ability to resist anoikis, thus enhancing their ability to migrate, reattach, and establish themselves in secondary sites (72,73). Catecholamines were found to protect ovarian cancer cells from anoikis, both in vitro and in vivo. These effects were mediated by focal adhesion kinase (FAK), a tyrosine kinase that promotes cell adhesion, which demonstrated increased activation (phosphorylation of $pFAK^{Y397}$) in response to NE. Clinically, elevated levels of $pFAK^{Y397}$ were observed in the tumor tissue of patients with ovarian cancer reporting depression and those with higher levels of tumor NE. Furthermore, phosphorylated FAK was linked to poorer overall survival in these patients (74). These data demonstrate another pathway by which β-adrenergic signaling can promote metastatic progression of cancer.

BIOBEHAVIORAL FACTORS AND CANCER PROGRESSION

Stress Effects on Stromal Cells in the Tumor Microenvironment

Tumor growth is, to a large extent, shaped and promoted or inhibited by signaling between tumor cells and the cells of the microenvironment. In addition to the effects of stress hormones on tumor cells, there are marked effects on host cells such as macrophages in the tumor microenvironment. Monocytes are drawn to the tumor microenvironment by tumor-derived chemotactic factors and then differentiate into macrophages. However, under the influence of the proinflammatory microenvironment, macrophages are induced to shift from their phagocytic phenotype to a protumor phenotype that produces tumor-promoting factors such as VEGF and MMPs, while simultaneously downregulating the cellular immune response by production of immunosuppressive cytokines such as IL-10 and tumor growth factor β (75–78). TAMs are thus directly involved in promoting angiogenesis, tumor proliferation, invasion, metastases, and downregulation of adaptive immunity. TAM infiltration is also associated with poorer survival (79–81). Both NE and cortisol have been shown to increase production of MMP-9 from monocyte-derived macrophages (54). In a preclinical orthotopic model of mammary cancer, stress-induced neuroendocrine activation had minimal effects on the primary tumor but showed profound effects on metastatic spread of the tumor to distant sites. These effects were mediated by β-adrenergic effects on macrophages, which induced changes in tumor gene expression supporting metastasis along with macrophage differentiation to a tumor-supporting phenotype (M2). These effects were blocked by propranolol and by suppression of macrophage activities. These findings demonstrate stress effects on tumor metastatic spread via tumor-macrophage signaling (82). In patients with ovarian cancer, biobehavioral risk factors that have been associated with higher NE levels, such as depression and stress (83), have been related to increased TAM secretion of MMP-9 (54). Thus, stress-related effects on TAM may have important implications for tumor progression by promoting a microenvironment that favors tumor growth.

BIOBEHAVIORAL RISK FACTORS AND TUMOR GENE EXPRESSION

Biobehavioral profiles have been linked to modulation of gene expression in pathways related to tumor progression in ovarian cancer. Tumors from patients with ovarian cancer with high levels of depression and low levels of social support (high risk) were compared with those patients reporting low levels of depression and high levels of social support (low risk) and matched for histologic diagnosis, stage, grade, and age. Compared with their low-risk counterparts, tumors from high-risk patients showed more than 200 upregulated gene transcripts, many of which are involved in tumor progression pathways (e.g., cyclic adenosine monophosphate response element-binding, nuclear factor-κB, STAT, ELK1). Furthermore, high-risk patients demonstrated elevated levels of intratumoral, but not plasma, NE. These findings point to a distinctive gene expression fingerprint in primary ovarian tumors of patients with high levels of depression and low levels of social support, with β-adrenergic signal transduction as a likely mediator of these relationships (84).

GLUCOCORTICOID DYNAMICS AND CANCER PROGRESSION

The previous sections highlight the role of adrenergic pathways in tumor progression. However, glucocorticoids can directly mediate processes promoting tumor growth as well. Cortisol has been shown to stimulate growth of prostate cancer cells (85) and enhance proliferation of human mammary cancer cells by nearly two-fold (86). In addition, glucocorticoids have been shown to directly enhance a survival pathway in mammary cancer cells (87) and downregulate expression of DNA repair genes (88). Glucocorticoids are also known to activate survival genes in cancer cells, which could inhibit chemotherapy-induced apoptosis (89–91). These effects may be relevant in the context of pharmacological glucocorticoids that are given as a part of many chemotherapy regimens. In a murine breast cancer model, social isolation induced an elevated corticosterone stress response, greater tumor burden, and alterations in gene expression in metabolic pathways that are known to contribute to increased tumor growth (92). Glucocorticoids are also known to inhibit the cellular immune response and thus are thought to decrease immunosurveillance in the context of cancer (93–95). Thus, glucocorticoids have direct effects on tumor growth and development, resistance to chemotherapy, and effects on immunosurveillance.

BIOBEHAVIORAL FACTORS AND INFLAMMATION

Inflammatory processes are common in epithelial tumors, and inflammation serves as a tumor initiator and promoter (96,97). Both tumor cells and TAMs produce substantial levels of inflammatory cytokines, particularly IL-6 (97). Inflammatory cytokines are also produced after cancer treatments such as radiation. Such tumor- or treatment-derived proinflammatory cytokines can potentially activate CNS pathways, evoking a syndrome of "sickness behaviors" comprising behavioral and affective responses that mimic flu-like vegetative symptoms (98–100). Preclinical studies have now shown that presence of tumor in itself can induce elevations in peripheral and central proinflammatory cytokines, as well as vegetative depressive-like behaviors (101,102). In clinical samples, fatigued breast cancer survivors have been shown to have chronic elevations in peripheral inflammatory markers accompanied by lower levels of serum cortisol and flatter diurnal cortisol slopes (103–106). Fatigue and debility in patients with ovarian cancer have been associated with cortisol dysregulation, in particular, with elevated levels of nocturnal cortisol (106). These findings suggest a tumor-to-brain pathway, in which tumor- and treatment-derived proinflammatory cytokines may contribute to chronic inflammation, ultimately resulting in sickness behaviors. It is also quite possible that chronic inflammation elicits increased

cortisol production for inflammatory control, thereby contributing to HPA axis dysregulation (107–109).

CONCLUSIONS AND FUTURE DIRECTIONS

There is converging evidence from in vitro, in vivo, and clinical studies, reviewed in brief above, that biobehavioral and stress-related processes are linked with critical elements of the metastatic cascade in both animal and human models. Contributions of systemic factors such as stress hormones to the signaling between tumor and stromal cells seem to be a key factor in modulating downstream pathways, with important implications for progression. This burgeoning area of research is beginning to reveal a coherent picture of physiological pathways implicated in cancer progression that are sensitive to modulation by neuroendocrine and stress-related pathways.

However, there are many important questions that still need to be addressed. Much of the research described previously has focused on patients with ovarian or breast cancer and preclinical models of ovarian and mammary cancer. It will be important to determine whether similar processes are evidenced in other cancers, for example, in nonsolid tumors such as leukemia and lymphomas. In addition, further specification of the downstream effects of particular psychological constructs is needed at the tumor level. In the clinical literature, lack of perceived social support is a factor that emerges repeatedly in associations with biological variables related to cancer progression, and social isolation has shown similar effects in the preclinical literature. Understanding what it is about social relationships that underlie these associations will be important in future research.

Additional questions include the following: How much stress, in terms of thresholds or chronicity, is needed to modulate tumor-related pathways? Are there windows of treatment (e.g., after surgery, after completion of treatment, after recurrence) when effects of biobehavioral risk factors might be most important? What are interactions of biobehavioral factors with diet, toxins, and metabolic factors or factors related to sex, race, and ethnicity? Do biobehavioral risk factors promote conditions that favor cancer recurrence? To what extent do effects of biobehavioral factors on the tumor microenvironment influence disease progression and survival? The relationship between depression and FAK in light of the link between high level of FAK and poor ovarian cancer survival discussed previously is suggestive in this respect. However, further examination of the clinical implications of these biobehavioral-disease marker relationships will be important in future research.

These findings highlight the importance of translational research to identify pathways relevant for biobehavioral influences on cancer biology. Understanding the mechanisms by which biobehavioral signaling can modulate fatigue, pain, and cognitive symptoms and influence the effectiveness of conventional therapies is an important direction for future research. Pharmacological approaches including β-blockers, antidepressants, and anti-inflammatory agents are potentially reasonable candidates for testing in light of the findings discussed previously. Psychosocial, mind-body, and complementary interventions may also modulate stress-related pathways implicated in tumor progression. A better understanding of biobehavioral mechanisms involved in cancer progression may help the development of personalized therapy by helping to characterize patients most likely to benefit from innovative intervention strategies.

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